CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ENDOSULFAN (THIODAN)

Chemical Code # 000259, Tolerance # 182
SB 950-052,
November 14, 1986
Revised 9/19/88; 3/15/90; 3/5/99; 12/3/03, 4/2/04

I. DATA GAP STATUS

Combined (chronic/onco), rat:	No data gap, possible adverse effect.
Chronic, dog:	No data gap, no adverse effect.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	No data gap, no adverse effect.
Teratogenicity, rat:	No data gap, no adverse effect.
Teratogenicity, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome aberration:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity, hen & rat:	No data gap, no adverse effect.

Note, Toxicology one-liners are attached
** indicates acceptable study

Bold face indicates possible adverse effect
File name: T040402

Revised: 3/15/90, 3/5/99, 12/3/03, 4/2/04 M. Silva.

All volumes through 106 and record numbers through 162457 have been examined.

II. TOXICOLOGY SUMMARY

COMBINED, RAT

Subchronic Study:

** 182 - 032 035803 "13 Week Toxicity Study in Rats Followed by a 4-week Withdrawal Period (Final Report)," (Barnard, A.V., Jones, D.R., Powell, L.A.J., Heywood, R., Street, A.E., Gibson, W.A., Gopinath, C., Majeed, S.K., Almond, R.H.; Huntingdon Research Centre plc, Huntingdon, Cambridgeshire, England, report # HST 230/84176, 3/25/85). Endosulfan technical (97.2% pure) was fed in the diet for 13 weeks at 0, 10, 30, 60, and 360 ppm (achieved intake male: 0.64, 1.92, 3.85 & 23.41 mg/kg; female: 0.75, 2.26, 4.59 & 27.17 mg/kg) with 25/sex/group. Following 13-weeks of treatment, 5/sex/group underwent a 4-week recovery (no treatment). Previously reported (Silva, 3/13/90) as having a NOEL of $\leq$ 0.64- M & 0.75- F (hematology), upon re-evaluation of effects that were not dose-related and/or were reversed after the recovery period (hematology and yellow discolored cells in kidneys), the NOEL was changed to 1.92 mg/kg- M and 2.26 mg/kg- F. The revised NOEL was based on: Enlarged kidneys in males at $\geq$ 3.85 mg/kg (at 3.85 mg/kg, the effect reversed during recovery); granular brown pigment in male livers and centrilobular enlargement of hepatocytes in both sexes at 23.41/27.17 mg/kg; kidney discoloration increased primarily at $\geq$ 3.85 (M) and $\geq$ 4.59 (F) -- reduced to trace amounts/reversed after 4 week recovery; granular/clumped pigment in males after recovery; packed cell volume decreased in males throughout treatment and recovery at 23.41 mg/kg; hemoglobin and RBCs decreased in both sexes at $\geq$ 3.85 mg/kg and in males at 23.41 mg/kg through recovery but reversed in females at recovery; mean corpuscular hemoglobin concentration decreased in both sexes at 23.41 mg/kg (M) and 27.17 mg/kg (F) throughout treatment and recovery; mean cell volume increased in males early in treatment and after recovery at 23.41 mg/kg and at $\geq$ 4.59 mg/kg throughout treatment and recovery in females; plasma and RBC ChE decreased at 27.17 mg/kg in females throughout treatment but reversed after recovery; increase in male brain weights at 23.41 mg/kg after recovery and at $\geq$ 4.59 mg/kg in females at treatment termination; livers enlarged in both sexes at treatment termination at 23.41 mg/kg (M) and 27.17 mg/kg (F) -- reversed after recovery; kidney weights increased in both sexes at treatment termination ($\geq$ 3.85 mg/kg-M & 27.17 mg/kg-F) and after recovery in males at 23.41 mg/kg; epididymal weights increased at 23.41 mg/kg at treatment termination; kidney weights in females and epididymal weights in males reversed after recovery. Acceptable. No adverse effect indicated. (M. Silva, 11/25/03)

Subchronic (Dermal) Rat

**** 182 - 062 073681** "Endosulfan - Water-Dispersible Powder (50%); Subchronic Dermal Toxicity (21 treatments in 30 days) in the Wistar Rat," (Ebert, E., Pharma Research Toxicology and Pathology, Frankfurt, Germany; 5/17/87, Laboratory Project ID #: 87.0664). Endosulfan water-dispersible powder 50% (49.5% a.i.) was administered dermally 21 times over 30 days (Mon - Fri) to SPF Wistar rats (6/sex/dose--Main group & 5/sex/dose--recovery group) at 0 (physiological saline), 40, 160, and 640 mg/kg (males) or 40, 80 and 160 mg/kg (females) to the shaved nape skin. Exposure was for 6 hours under an occlusive bandage. The recovery group (all doses except 40 mg/kg) was observed for 22 days after the final dermal treatment. Subchronic NOEL = 40 mg/kg, M & F (A female at 80 mg/kg had dacryohemorrhea and a blood-crusted snout day 22. At 80 mg/kg 1/11 females and at 160 mg/kg, 3/11 females died. Treated skin showed a dose-related increase in irritation (dry, chapped, scaley) in both sexes (reversed by week 3). Males at 640 mg/kg and females at 160 mg/kg had statistically significantly

decreased body weight gain. There was an increase in reticulocytes in males at ≥ 160 mg/kg and in females at 160 mg/kg. Males had decreased protein and α2-globulin at 640 mg/kg and females had a decrease in GOT at 160 mg/kg. After recovery, males had decreased potassium at 640 mg/kg. Macro and microscopically there was an increase in yellow coloration and in sperm granulomas in the epididymides at ≥ 160 mg/kg and at 640 in the recovery group.) ChE NOEL = Males 160 mg/kg, Females 40 mg/kg (Males had statistically significantly decreased serum ChE at 640 mg/kg (-13%) and in females at 80 mg/kg (-28%) and 160 mg/kg (-46%). Brain ChE in males was increased 15% at 640 mg/kg. No effects were observed in males at recovery. Females showed decreases in serum ChE at 80 mg/kg (-24%). Recovery females had decreased serum ChE (23%, statistics not performed on 3 surviving females). This study is acceptable, with a possible adverse effect (increased epididymal pathology in males.) M. Silva, 4/2/04.

Combined Study:

** **066 074851**, "Combined Chronic Toxicity/Carcinogenicity Study 104-Week Feeding in Rats", (Huntingdon Research Centre Ltd., England, report # HST 289/881067, 4/1/89). Endosulfan technical (96.7% pure; batch 381 (A-D)) was fed in the diet for 104 weeks at 0 (vehicle = acetone to dissolve, then corn oil to mix in diet), 3.0, 7.5, 15.0, and 75.0 ppm to 70 Crl:CD (SD) BR rats/sex/group (20/sex/group as satellites for blood sampling and evaluation of toxicity). Chronic NOEL = 15 ppm (reduced bodyweight gain (8% to 18% less than controls) in both sexes at 75 ppm; increased number of enlarged kidneys in females at 75 ppm). **Adverse effect**: **increased incidence of aneurysms in blood vessels and an increased incidence in progressive glomerulo-nephrosis in males at 75 ppm**. Oncogenicity NOEL ≥ 75 ppm. **Acceptable**. (H. Green & M. Silva, 3/8/90).

CHRONIC, RAT (see combined rat, above)

042 047297, Summary of 1959 study conducted at Hazleton. Rats were fed 0, 10, 30 or 100 ppm for 104 weeks. Kidney damage in males at 100 ppm is reported but the adverse effect cannot be assessed from the summary paragraph.

CHRONIC, DOG

065 074850, "Testing for Toxicity by Repeated Oral Administration (1-year feeding study) to Beagle Dogs", (Hoechst Aktiengesellschaft, Pharma Research, Toxicology and Pathology, 6230 Frankfurt (M) 80, West Germany, Report # 89.0188, 1/20/89). Endosulfan technical (96.5% pure) was fed in the diet for 1 year at 0, 3, 10, 30, and 30/45/60 ppm (54 days at 30 ppm, 52 days at 45 ppm, and 19-40 days at 60 ppm) to 6 Beagle dogs/sex/dose. All dogs at 30/45/60 ppm were sacrificed by treatment day 147 due to onset of nervous symptoms after dose was increased to 60 ppm. **No adverse effect. NOEL = 10 ppm (After day 135, at intervals, 3 males and 2 females at 30 ppm experienced violent contractions of the upper abdomen and convulsive movement (males) beginning 2 1/2 to 6 hours post-administration). **Acceptable**. (H. Green & M. Silva, 3/5/90).

041 045581, "One Year Repeated Oral Administration of Thiodan Technical in Dogs; Final Report." (5/12/59, Hazleton Labs, NCT 252-33) Endosulfan (technical, no purity stated, Lot # MR 3931), given orally in capsules at 0, 0.075, 0.25 and 0.75 mg/kg/day for 1 year, dosed 6 days a week (the 0.075 mg/kg/day group received 2.5 mg/kg/day for the first three days); no observed effects noted at any dose; only 2 dogs/sex/dose; lacks complete serum chemistry and histopathological analyses; incomplete,

unacceptable, not upgradeable. No dose-related observable toxic effects. (G. Patterson, 9/12/86) No EPA one-liner.

ONCOGENICITY, RAT (see combined rat, above)

012 008617 (1984, Hoechst Aktiengesellschaft) Correspondence - no data.

007 921663, "Bioassay of Endosulfan for Possible Carcinogenicity." (1978, Hazleton for NCI) Endosulfan, technical, 98.8%; fed in the diet to 20/sex for controls and 50/sex/test group, Osborne-Mendel rats; fed at 0, 408 or 952 ppm (time-weighted average, males) and 0, 223 or 445 ppm (time-weighted average, females) for 73 - 81 weeks; high mortality in treated males - cannot determine a NOEL; onco NOEL (females) > 445 ppm (TWA); systemic NOEL < 408 **Adverse effects** indicated: males for kidney chronic inflammation, toxic nephropathy and associated calcium deposition in kidneys and other tissues, parathyroid hyperplasia and testicular atrophy - seen in both test groups. **Unacceptable,** not upgradeable (high mortality in both test groups of males precluding any useful oncogenicity data, inadequate number of matched controls, no analysis of diet, dose selection with numerous changes in all groups, housing of animals in same room with other studies using toxic substances, no hematology, no individual data). (Gee, 11/14/86)

042 47299 Summary of 921663.

ONCOGENICITY, MICE

064 075035, "Carcinogenicity Study in Mice, 24 Month Feeding Study", (Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, F.R.G., 4/6/88). Endosulfan technical ($\underline{\geq}$ 97.1% pure) was fed in the diet for 24 months at 0 (sesame oil), 2, 6, and 18 ppm to 80 NMRI Hoe:NMRKf (SPF71) mice/sex/group (with interim sacrifices of 10/sex/group at 12 and 18 months). **No adverse effect. Oncogenicity NOEL $\underline{\geq}$ 18 ppm (an oncogenic effect was not observed). Chronic NOEL = 6 ppm (reduced bodyweight gain (approximately 5% reduction) reported in main group males at 18 ppm; increased mortality reported in main group females at 18 ppm). **Acceptable**. (Green & Silva, 3/9/90).

007 035628, "Bioassay of Endosulfan for Possible Carcinogenicity." (Hazleton, 1978, for NCI) Endosulfan, technical, 98.8%; fed to 20/sex in controls and 50/sex/test group - B6C3F1 mice - at 0, 3.5 or 6.9 ppm (time-weighted average, males) and 0, 2.0 or 3.9 ppm (time-weighted average, females) for 73 weeks followed by 14 weeks on control diet; onco NOEL (females) > 3.9 ppm (TWA); cannot determine NOEL for males due to high mortality in test groups. Unacceptable (high mortality in males precluding useful data, inadequate number of matched controls, housing of mice in same room with those on other studies with toxic materials with a possiblity of cross-contamination, no individual data, no analysis of diet, dose selection.) Gee, 11/14/86.
042 047300, Summary of 035628.

012 008617, (1984, Hoechst Aktiengesellschaft) Correspondence- no data.

REPRODUCTION, RAT

002 921665 -68, (1966, IBT) JPC, 3/28/85. Non-validated IBT study; no EPA one-liner.

012 008613, (1984, Hoechst Aktiengesellschaft) Correspondence - no data.

022 035789, "Effect of Endosulfan-Technical (Code: HOE 02671 0 I AT209) on Reproductive Function of Multiple Generations in the Rat." (1984, Huntingdon HST 204/83768). Endosulfan, 97%; two generation study at 0, 3, 15 and 75 ppm; **no adverse effects on reproduction; marginal decrease in litter weight at 75 ppm; organ weights of liver, kidney increased at 75 ppm without histopathology to confirm. **Acceptable**. A preliminary study in 023. No EPA one-liner. Parental NOEL = 15 ppm. (Gee, 10/25/85)

023 035790, (1982, Huntingdon) J. Gee, 10/25/85. Addendum to 022 035789.

024 035791, (1985, Huntingdon) J. Gee, 10/25/85. Addendum (histopath) to 022 035789.

037 036881, (no date given, FMC) Summary of 022 035789.

TERATOLOGY, RAT

026, 057 017686, 060606, "Teratology Study with FMC in Rats." (Raltech, 10/2/80, Study No. 79041) Endosulfan, 97.3%; dose levels were 0 (corn oil), 0.66, 2.0 or 6.0 mg/kg/day by oral gavage; 25/group, Sprague Dawley rats; maternal NOEL = 2 mg/kg/day (decreased body weight gain and increased clinical signs at 6 mg/kg/day. Developmental NOEL = 2 mg/kg/day (developmental toxicity, growth retardation is evident at 6 mg/kg/day). **No adverse effect. Initially reviewed as incomplete (JPC, 3/28/85 and JAP, 11/15/86) because of lack of analyses of dosing solutions and dose justification. Record 060606 is a retrospective study for content, homogeneity and stability in corn oil. Record 060605 (see below) is a range-finding study for dose selection. The collective data are upgraded to **acceptable** status with no adverse developmental effect. (Gee, 9/19/88)
EPA 1-liner: Minimum. Teratogenic NOEL = 6 mg/kg (the teratogenic effects noted were accompanied by frank maternal toxicity.) Maternal NOEL = 2 mg/kg (reduced body weight, hyperactivity, rough coat, flaccidity and brown exudate.) Fetotoxic NOEL = 2 mg/kg (skeletal, visceral and external anomalies; decrease in pup size and weight.)

037 036884, (1985, Hazleton [formerly Raltech]), This record contains historical control data for the rat teratology study found in 009, 026 017686. Note: The second review changes the earlier finding of adverse effect in 009 017686 to a finding of **no adverse effect**. (JAP, 5/6/86)

057 060605, "Range-finding Study with FMC 5462 in Pregnant Rats", (Raltech Scientific Services - now Hazleton, Study No. 79031, 10/8/80), Endosulfan, 97.3%, given by oral gavage at 0 (corn oil), 1.25, 2.5, 5, 10, 20 or 40 mg/kg, days 6 - 19 of gestation, CD Sprague Dawley rats, 6 per group except 1 only at 40 mg/kg; all died at 20 and 40 mg/kg, 4/6 at 10 mg/kg; clinical signs at all doses including salivation, piloerection, poor muscle tone, hyperactivity, tremors and convulsions. **Supplementary** data for CDFA # 017686. (Gee, 9/19/88)

003 921664, (1980, Raltech) One page summary of 026 017686.

010 021600, (1980, Raltech) Nine page summary of 026 017686.

037 036882, (No date given, FMC) Half page summary of 026 017686.

037 036883, (1981, EPA) Evaluation of study in 026 017686.

041 045580, (1985, Hazleton) Exact duplicate of historical control data in 037 036884.

012 008616, (1984, Hoechst Akiengesellschaft) Correspondence - no data.

TERATOLOGY, RABBIT

037 036880, (No date given, FMC) Summary of 027 035798.

027, 057 035798, 060607, "Teratology Study with FMC 5462 in Rabbits." (Raltech, 7/27/81, Study No. 80070, FMC A79-370) Endosulfan, 97.3%; given by oral gavage to New Zealand White rabbits, days 6 - 28 of gestation; 0 (corn oil), 0.3, 0.7 or 1.8 mg/kg/day, 20 - 26 per group; minimal maternal toxicity at 1.8 mg/kg; NOEL = 0.7 mg/kg/day; no developmental toxicity at any level tested. **No adverse effect indicated. Initially reviewed as unacceptable but upgradable (missing analysis of dosing solutions and justification of dose selection), JAP, 11/15/85. CDFA Record # 060607 contains analyses of dosing solutions for content, stability in corn oil and homogeneity. CDFA Record # 060604 reports on a second range-finding study justifying dose selection. The collective data are upgraded to **acceptable** status. (Gee, 9/19/88)

041 045582, "Final Report: Range-Finding Study with FMC 5462 in Pregnant Rabbits." (12/30/81, Raltech Study No. 79032), Endosulfan (technical, 97.3%), teratogencity range-finding study in rabbits, given by oral gavage at 0, 0.5, 1.0 and 2.0 mg/kg in corn oil and at 0, 0.625, 1.25, 2.5, 5.0, 10.0, 20.0, 40.0 and 80.0 mg/kg in corn oil; volume of corn oil had an effect on observed signs of toxicity; no survivors in 5.0 mg/kg and above groups, mortality 2/6 in 2.0 mg/kg and 0/6 in 1.0 mg/kg group with signs of maternal toxicity present. Submitted as justification for dose selection in the rabbit teratology study reviewed above (# 035798). The doses, however, do not match those stated on pg. 79, Amendment No. 4, of the submission which states Study No. 79032 was conducted with doses of 0, 1, 2, 4, 8 and 12 mg/kg. (Patterson, 9/19/86)

057 060604, "Range-Finding Study with FMC 5462 in Pregnant Rabbits (Supplier: Dutchland Laboratories, Inc.) Raltech Study No. 79032." (Raltech Scientific Services, WI, 12/30/81), Endosulfan, 97.3%, given by oral gavage to New Zealand White rabbits, days 6 - 28 of gestation, 3 - 10 per group, at 0 (corn oil), 1, 2, 4, 8 or 12 mg/kg/day; no survivors at 8 and 12 mg/kg/day, 4/8 at 4 mg/kg (2 may have been misinjection); clinical neurotoxic signs at 2 mg/kg and above; decreased weight gain at 4 mg/kg; dose justification for full study, CDFA # 035798; no report on fetal findings. **Supplemental** data. (Gee, 9/19/88)

MUTAGENICITY, GENE

Mammalian systems

025 035792, "Mutagenicity Evaluation of HOE 002671-Substance Technical in the Mouse Lymphoma Forward Mutation Assay - Final Report." (1984, LBI, Project 20989), Mouse lymphoma L5178Y TK+/-

cells; endosulfan - 97.2%; 0, 6.25, 12.5, 18.8, 25.0, 37.5, 50, 75 or 100 ug/ml, four hours; with and without rat liver activation; **no increase in mutation frequency**; no repeat experiment to confirm. **Unacceptable** (no repeat trial). Gee, 10/24/85. No EPA one-liner.

042 047291 and 047294, (FMC, 6/26/86). Rebuttal to review of 035792. Objection of no repeat trial in mouse lymphoma assay stands. Record # 047294 presents hydrolysis data which are useful. (J. Gee, 11/12/86)

Microbial systems

025 035796, "Study of the Mutagenic Activity "in vitro" of the Compound Endosulfan - Technical (Code HOE 002671 0I 0003) with Schizosaccharomyces pombe." (1984, RBM, Italy), Schizosaccharomyces pombe ade biosynthetic pathway; endosulfan, technical, 97.2%; 0, 62.5, 125, 250 or 500 ug/ml, four hours; **no effect in mutation frequency** is reported. **Unacceptable** (no repeat experiment, no justification of high concentration). (Gee, 10/24/85) No EPA one-liner.

042 047306, "Microbial Mutagenicity Testing on Endosulfan.", (Institute of Environmental Toxicology, Japan, 1978), Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation at 0, 5, 10, 50, 100, 500, 1000 or 5000 ug/plate in duplicate, single trial; **no increase in reversion rate** reported; **Unacceptable** (single trial - otherwise, a good report). (Gee, 11/12/86)

SUMMARY: Although there is no single test report which meets guidelines, there are three different tests (2 in microbial systems and one in mammalian) showing no mutagenic effect. The major problem with the three tests is no repeat trial was performed to confirm the negative response. If taken together, the data gap may be considered filled based on use of the three test systems to confirm each other. (Gee, 11/14/86)

MUTAGENICITY, CHROMOSOME

025 035794, "Micronucleus Test in Male and Female NMRI Mice Following Oral Administration.", (10/1983, Hoechst), Endosulfan, 97.2%; Mouse bone marrow micronucleus test, two doses by oral gavage; sampling of 5 males and 5 females at six hours only, 0, 0.2, 1.0 or 5.0 mg/kg; **no increase in micronuclei or change in PCE/NCE** was noted. **Unacceptable** (one sampling only at six hours). (Gee, 10/24/85) No EPA one-liner.
042 047292, Rebuttal to review of 035794 and includes statement that Hoechst will conduct another micronucleus study following EPA guidelines - no date indicated for completion.

042 047313, "Mutagenicity Studies involving Aldrin, Endosulfan, Dimethoate, Phosphamidon, Carbaryl and Ceresan.", (Osmania Univ., Hyderabad, India, published in Bull. Environm. Contam. Toxicol. 25: 277-282 (1980). Mouse micronucleus test. Endosulfan, no purity stated; given orally (in diet) at 0 or 43.3 mg/kg to 4 male mice in two daily doses with sacrifice 6 hours after second dose. 2000 polychromatic erythrocytes and normochromatic erythrocytes were scored for each animal; **no adverse effect** is reported (% of control PCE's with micronuclei was 0.28 and 0.52 for test group). **Unacceptable,** not upgradeable (single sex, single dose with no justification and no clinical obs reported, no indvidual data, protocol with single sacrifice time). (Gee, 11/13/86)

042 047309, "Mutagenic Study with Thiodan in Albino Mice", (IBT, 1972, E1057B) EPA lists the report as "valid" but CI (core invalid) for data requirement and as "replaced". Endosulfan technical, 98%; given to 12 male mice per group by i.p. injection at 0, 5 or 10 mg/kg b. wt.; mated 1:3 for 6 weekly periods; no deaths in treated groups; **no dominant lethal effect** reported. **Unacceptable,** not upgradeable (no individual data, fewer than 30 pregnant females per group, dose selection - two doses only and questionable if reached m.t.d.) (Gee, 11/13/86)

042 048638, "Endosulfan, Substance Technical, Chromosome Aberration in Human Lymphocytes Cultured in vitro", (RBM - Inst. di Ricerche Biomediche, Torino, Italy, 1986), Endosulfan technical, 97.9%; human lymphocytes from a male volunteer were stimulated with phytohemagglutinin (PHA), exposed for 4 hours to 0, 1, 10, 100 or 200 ug/ml with and without rat liver activation and scored after 23 additional hours (the last three with colchicine) for chromosomal aberrations and mitotic indices; 200 ug/ml was toxic. **Acceptable with **no positive findings**. (Gee, 11/13/86)

042 047312, "Endosulfan: Lack of Cytogenetic Effects in Male Rats." (Industrial Toxicology Research Centre, India, 1978, published in Bull. Environm. Contam. Toxicol. 20: 826-833 (1978). Endosulfan, no purity stated; given to 8 male rats per group by oral gavage at 0, 11, 22, 36.6 or 55 mg/kg b. wt.; bone marrow and spermatogonial cells were analyzed for aberrations 4 hours after colchicine injection. **No adverse effects** indicated. **Unacceptable**, not upgradeable (single sex, no data). (Gee, 11/13/86)

MUTAGENICITY, DNA

025 035793, "Evaluation of HOE 002671-Substance Technical in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay - Final Report", (1984, LBI, project 20991), Primary rat hepatocytes, unscheduled DNA synthesis; endosulfan - technical grade (purity not stated); 0, 0.102, 0.255, 0.510, 1.02, 5.10, 10.2, 25.5 or 51.0 ug/ml; toxic at 51.0; triplicate cultures. **No detectable increase in grains/nucleus at any concentration. **Acceptable.** (Gee, 10/24/85)
No EPA one liner.

025 035795, "Study of the Mutagenic Activity of the Compound Endosulfan - Technical with Saccharomyces cerevisiae." (1984, RBM, Italy), Endosulfan, 97.4%; Saccharomyces cervisiae D4 diploid strain, 0, 100, 500, 1000 or 5000 ug/ml, four hours, with and without activation, assayed ade and trp, **no increase in mutation was detected; DMSO as solvent; no repeat experiment; four plates per concentration. **Acceptable**. (Gee, 10/24/85)
No EPA one-liner.

012 008614, (1984, Hoechst Aktiengesellschaft) Correspondence - no data

042 047306, "Microbial Mutagenicity Testing on Endosulfan", (Inst. of Environmental Toxicology, Japan, 1978), Bacillus subtilis; endosulfan, 99%, strains H17 and M45, tested without activation at 0, 20, 100, 200, 500, 1000 or 2000 ug/disk in 20 ul, 1 plate per concentration, kanamycin and mitomycin C as controls; no difference in growth between strains and no cytotoxicity - therefore, a "no test". **No adverse effect** indicated. **Unacceptable** (no activation, no justification for concentrations used). Not upgradeable. (Gee, 11/13/86)

NEUROTOXICITY

028 035799, "Acute Delayed Neurotoxicity Study with Endosulfan Technical (Code: HOE 002671 0I Z097 0003) in the Domestic Hen." (1983, Huntingdon) Hens - domestic; endosulfan - 97.2%; 96 mg/kg with atropine - 2-PAM to protect at LD50; redosed in 21 days; histopathology on 9 of 17 survivors of initial 40 birds; **no compound related delayed neuropathology is reported. Acceptable. Rebuttal by FMC, 182-042, # 47293, contains statement that Huntingdon guaranteed adequate pen space to observe gait of hens and that FIFRA guidelines state a minimum of 6 hens must survive for histopathological examination. Reconsideration of the initial finding of the study as unacceptable based on 10 hens per pen and not all survivors examined (9/17), changes the report to **acceptable**. (Gee, 10/24/85 and 11/12/86)

** 106 162457 "Neurotoxicological Screening in the Male and Female Wistar Rat; Acute Oral Toxicity," (Bury, D.; Hoechst Marion Roussel, Preclinical Development Germany, Drug Safety, FRG; Study #: 96.0373; Report #: 97.0149; 7/7/97). Endosulfan technical (98.6% pure) was administered by oral gavage (single dose) to fasted Wistar rats (10/sex/dose) at 0, 6.25, 12.5, 25, 50 and 100 mg/kg (males) and 0, 0.75, 1.5, 3, 6 and 12 mg/kg (females). The vehicle was 2% starch mucilage (potato starch in deionized water), the stability of endosulfan in the vehicle was for 4 hours and the duration of observation was 15 days. The neurotoxicological screening (Functional Observational Battery & motor activity) was performed 7 days prior to treatment initiation and 14 days post-dosing. Three weeks post-dosing, controls (10/sex) and 5/sex (all other doses except 4/sex at 100 mg/kg) were terminated for neuropathological examination. SYSTEMIC NOEL = 12.5 mg/kg (males) & 1.5 mg/kg (females) (There was an increase in clinical signs in males at $\geq$ 25 mg/kg and in females at $\geq$ 3 mg/kg, which lasted for 1 day.) Acceptable. No adverse effect. M. Silva, 2/18/99.

104 162455 "Acrylamide: Neurotoxicological Screening in Rats--Positive Control Study," (Bury; Hoechst AG, Frankfurt, FRG; 4/11/95). This volume contains a positive control recommended for acute neurotoxicity studies performed in rat. No worksheet. M. Silva, 3/3/99.

103 162456 "Carbaryl: Neurotoxicological Screening in Rats--Positive Control Study," (Bury; Hoechst AG, Frankfurt, FRG; 3/27/95). This volume contains a positive control recommended for acute neurotoxicity studies performed in rat. No worksheet. M. Silva, 3/3/99.

082 126557 "Endosulfan - Active Ingredient Technical: Testing for Subchronic Dermal Toxicity (21 applications over 30 days) in Wistar Rats," (Ebert, Leist and Kramer; Hoechst, AG, FRG; 2/22/85, Study #: 83.0508). Endosulfan technical (97.2% pure) was administered dermally 21 times over 30 days (Mon - Fri) to Wistar rats (6/sex/dose) at 0 (sesame oil), 1, 3, 9, 27 and 81 (males only) mg/kg to the shaved nape skin. Exposure was for 6 hours under an occlusive bandage. Systemic NOEL = 1 mg/kg (Pathological effects were observed in livers of both sexes at $\geq$ 3 mg/kg. Mortality was observed in males at 9 & 81 mg/kg and in females at 27 mg/kg. Clinical signs in animals that died were increased salivation, blood-encrusted nose, passivity, dyspnea, tono-clonic convulsions and increased respiratory rate.) ChE NOEL < 1 mg/kg (There was a significant decrease in serum ChE in males at $\geq$ 9 mg/kg, however this decrease was also observed in females at the same dose. Brain ChE was decreased in both sexes at all doses (significant in females at all doses, in males at $\geq$ 3 mg/kg). No adverse dermal effect. These data are supplemental. M. Silva, 2/24/99.

083 126558 "Endosulfan - Active Ingredient Technical: Testing for Subchronic Dermal Toxicity (21 applications over 30 days) in SPF Wistar Rats," (Ebert, Weigand and Kramer; Hoechst, AG, FRG;

3/11/85, Study #: 83.0118). Endosulfan technical (97.2% pure) was administered dermally 21 times over 30 days (Mon - Fri) to SPF Wistar rats (6/sex/dose--Main group & 5/sex/dose--recovery group) at 0 (sesame oil), 12, 48, 96 and 192 mg/kg (males) or 3, 6, 12 and 48 mg/kg (females) to the shaved nape skin. Exposure was for 6 hours under an occlusive bandage. The recovery group was observed for 14 days after the final dermal treatment. Systemic NOEL = Males = 48 mg/kg; Female = 6 mg/kg (Females at $\geq$ 12 mg/kg showed pilo-erection, increased salivation and lacrimation. At 48 mg/kg, females also showed blood-encrusted nares and dacryohemorrhea and 4/6 females died between days 2 & 22 following tono-clonic convulsions. Males at 192 mg/kg died (1/6-day 6 & 1/6-day 9). Liver and kidney pathology was observed in males at 192 mg/kg (high dose) and in females at 48 mg/kg (high dose).) ChE NOEL = 48 mg/kg (Serum at 192 mg/kg and brain ChE at 96 mg/kg were significantly decreased in males immediately after treatment. No differences were observed after the recovery period.) No adverse dermal effect. These data are supplemental. M. Silva, 2/26/99.

084 126577 "Endosulfan - Active Ingredient Technical: Testing for Subchronic Inhalation Toxicity (21 exposures in 29 days) in SPF Wistar Rats," (Hollander, Weigand and Kramer; Hoechst, AG, FRG; 8/15/84, Study #: 84.0103). Endosulfan technical (97.2% pure) was administered by inhalation (aerosol, nose only) 21 times over 29 days (Mon - Fri, 6 hours/day) to Wistar rats (15/sex/dose) at 0 (air only), 0 (ethanol - polyethylene 400 (1:1)), 0.5, 1.0 and 2.0 ug/L air. Following the 29 day treatment period, 10/sex/dose were terminated and the remaining 5/sex/dose were observed over a 29 day recovery period. NOEL = 1.0 ug/L (One/10 males at 2.0 ug/L showed poor condition from day 12 until termination. Signs were emaciation, pale skin, squatting position and high-legged position. Bodyweight gains were decreased in males at 2.0 ug/L from day 20 of treatment (not significant). On day 20 of treatment, males showed a significant decrease in food consumption at 2.0 ug/L. Relative water consumption was slightly increased from days 9 to 24 in males at $\geq$ vehicle control (including 0.5, 1.0 & 2.0 ug/L), when compared to air only control. Clinical chemistry for females showed significant (but reversible) effects in chloride, calcium, creatinine and SGOT at 2.0 ug/L.) No adverse inhalation effect was observed. These data are supplemental. M. Silva, 3/2/99.

ADDITIONAL STUDIES AND SUPPLEMENTAL LITERATURE

Volume 182-008 contains the 1982 EPA registration standard.
081 126555 "Progress Report for: Acute Oral Administration (rats); Acute Dermal Application (rabbits) & Acute Eye Application (rabbits)," (Elsea, J.R., Hazleton Laboratories, Falls Chruch, VA; 1/11/57). This volume contained summarized protocols and data for acute oral, dermal and eye application studies performed with endosulfan technical in rats and rabbits. Acute Oral: Male albino rats (5/dose) were gavaged with 10.0, 21.5, 46.4, 100, 215 and 464 mg/kg endosulfan. Rats were observed for 7 days after dosing (Time = 0, 1, 2, 4, 24 hours & 2, 3, 4, 5, 6 & 7 days). The NOEL = 10.0 mg/kg, LD_{50} = 110 mg/kg and clinical signs ranged from slight depression, preening, salivation, exessive masticatory movements, lacrimation, exophthalmia and rapid, labored respiration to bloody nasal discharge, ataxia, sprawling of the limbs, tremors, depressed or absent righting, placement and pain reflexes and Straub-like tails. Death was immediately preceded by phonation, tonic and clonic convulsions, gasping and coma. Autopsies for animals which died on study showed hyperemic or hemorrhagic lungs, irritation of the small intestine and congested kidneys and adrenals. Acute Dermal: Albino rabbits (4/dose) were treated dermally, under occlusion, with technical endosulfan (cotton-seed oil) at 0, 46.4, 100, 215, 464 and 1000 mg/kg for 24 hours. Rabbits were observed for 7 days post-dosing (Time = 0, 1, 2, 4, 24 hours & 2, 3, 4, 5, 6 & 7 days). NOEL = 46.4 mg/kg, LD_{50} =

359 mg/kg and clinical signs showed diarrhea, lacrimation rapid and labored respiration, slight spreading of the limbs, depression, excessive ambulatory movements, tremors, depressed or absent righting and placement reflexes, inability to hold the head erect, running movements of the limbs, phonation and tonic & clonic convulsions. There was slight irritation or erythema at each dose which subsided in surviving animals at 1-4 days. At higher doses, slight atonia and/or slight desquamation during the final 3-4 days was observed. Autopsies for animals which died on study showed congested lungs containing hemorrhagic areas, granular-appearing livers, irritation of the large intestine and congested kidneys. Acute Eye: A group of 3 albino rabbits was treated at 3.0 mg/kg in the conjunctival sac of the left eye of each rabbit. Treated eyes were held closed for 30 seconds following application after which an immediate reading was made. Observations were performed at 1, 4 & 24 hours and daily for the next 6 days. Very mild eye irritation was noted (slight erythema, vascularization of sclera and nictitating membrane & lacrimation) which subsided at 24 hours. No adverse effects on these studies. No worksheets. These data are supplemental. M. Silva, 3/4/99.

081 126556 "Testing of the therapeutic effect of diazepam (Valium®) and phenobarbital (Luminal®) in the event of acute poisoning with endosulfan - active ingredient technical (Code: Hoe 002671 OI ZD97 0003) in Wistar rats," (Ebert & Weigand; Hoechst AG, Frankfurt, FRG; Study #: 83.0114; 5/2/84). Female Wistar rats were treated orally with a single lethal dose (80 mg/kg; 97.2% pure) of endosulfan (vehicle = 2% starch solution). Approximately10-20 minutes after the endosulfan treatment, the animals received the following (see table, next page):

Endosulfan (mg/kg)	Therapeutic Agent	Endosulfan Doses (mg/kg)		Treatment Route	# Rats
		Initial	Final		
80	--	--	--	--	20
80	Diazepam	2	--	i.p.	5
80	Diazepam	2	2	i.p.	5
80	Diazepam	20	20	i.p.	5
80	Diazepam	60	--	i.p.	10
80	Phenobarbital	50	10	i.p.	10
80	Phenobarbital	70	20	i.p.	10
80	Phenobarbital	70	10	i.p.	10

Subsequent doses were administered before occurrence or after subsidence of the convulsive phase, by the following scheme:

Endosulfan (mg/kg)	Therapeutic Agent/Antidote	Initial 10-20 min	Subsequent 1-6 h	1-6 d	Lethality After Time (hours) 2 h	4 h	6 h	1 d	7 d	14 d	# Rats
80	0 (endosulfan)	--	--	--	12	19	19	20			20

80	Diazepam	2	--	--	0	2	4	5			5
80	Diazepam	2	2	--	0	3	4	5			5
80	Diazepam	20	20	--	0	2	3	4	4	4	5
80	Diazepam	60	--	--	0	3	4	10			10
80	Phenobarbital	50	10	--	0	3	5	5	7	7	10
80	Phenobarbital	70	20	--	2	3	3	3	6	6	10
80	Phenobarbital	70	10	10*	1	3	5	5	5	5	10

* = Daily

Although diazepam has anticonvulsive properties it provided only a delay in the lethality of endosulfan, rather than a therapeutic effect. Phenobarbital (anti-epileptic) proved to be an effective therapeutic agent for reducing clinical signs of endosulfan intoxication and lethality rate. These data are supplemental. M. Silva, 3/5/99.